PATENT
0020-4710P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	YAMANOUCHI, Masaya et al.	Conf.:	9841
Appl. No.:	09/578,693	Group:	1641
Filed:	May 26, 2000	Examiner:	L. Cook
For:	METHOD FOR EXAMINING HUMAN KIDNEY DISEASE BY DETECTING THE FATTY ACID BINDING PROTEIN		

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
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Sir:

I, Takeshi SUGAYA, a citizen of Japan residing at Itami-shi, Hyogo-ken, Japan, hereby declare as follows:

1. I am a co-inventor of the subject matter of the above-referenced patent application.

2. I graduated from the Faculty of Engineering of Kyoto University, Japan in March 1986. I also received my Masters degree in Engineering from Kyoto University in March 1989 and my Ph.D from the University of Tsukuba in November 1999.

3. From April 1989 to date, I have been employed by Tanabe Seiyaku Co., Ltd., Osaka, Japan, the assignee of the

above-identified application. From April 1989 until October 2000 I was engaged in research works in the fields of biochemistry and pharmacology at research laboratories of Tanabe Seiyaku Co., Ltd. From November 2000 to present, I have been on loan to CMIC Co., Ltd., Tokyo, Japan, an outsourcing pharmaceutical development company, one of the Contract Research Organizations (CROs). At CMIC Co., Ltd., I have been engaged in research and development of diagnostic reagents, and methods and systems including the same in the field of diagnosis of renal disease directed by L-FABP. My present position is as the project leader of business development at CMIC Co., Ltd.

4. I am the co-author of about 53 papers in the field of cardiovascular and nephrology, and a co-author of 5 papers (one being still in press) in the field of diagnosis of renal disease focused on L-FABP. I received the young investigator award from the Society of Japan Cardiovascular Endocrinology and Metabolism in 1997. Since January 2005 to present, I was delegated as a guest professor at the department of Nephrology and Hypertension at St. Marianna University School of Medicine, Japan.

5. I have read and understood the contents of U.S. patent application no.: 09/578,693 and am familiar with the prosecution history of said application.

6. The foregoing remarks and objective evidence are presented to show that the claimed invention satisfies a long-felt need in the art, which was recognized, persistent, and not solved by others until conception and reduction to practice of the presently claimed invention. For this reason, the claimed invention is novel and non-obvious over the prior art.

7. The need for a method for the diagnosis or prognosis of kidney disease in a human is a persistent one that is recognized by those of ordinary skill in the art. The American Heart Association Science Advisory and Coordinating Committee states that kidney disease is a worldwide public health problem. *See*, Sarnak et al., "AHA Scientific Statement: Kidney disease as a risk factor for development of cardiovascular disease," *Circulation*, 108:2154-2169, October 28, 2003 (attached hereto as **Exhibit A**). As described in the Scientific Statement, chronic kidney disease is a major health problem facing the world today, and the care and treatment of

patients suffering from kidney disease imposes a terrible economic burden on society.

In the United States, for example, the number of individuals with kidney failure treated with dialysis and kidney transplantation exceeded 320,000 in 1998, and continues to increase. At the present time, the prevalence of patients in the early stages of chronic kidney disease is even greater. The Scientific Statement also states that cardiovascular disease (CVD) is frequently associated with kidney disease, and that patients with kidney disease associated with CVD tend to die of CVD. Thus, the diagnosis/prognosis of kidney disease is also very important as viewed as a risk factor for CVD. *See*, AHA Scientific Statement, page 2154, left column.

Since kidney disease has become and is a major worldwide public health problem, a method for the diagnosis/prognosis of kidney disease has taken on a great importance in society. However, prior to the present invention, no sufficient technology for the diagnosis/prognosis of kidney disease has been developed. For example, as described in Levin, "Consequences of late referral on patient outcomes," *Nephrol. Dial. Transplant*, 15(Suppl.3):8-13, 2000 (attached hereto as **Exhibit B**), the identification of patients in the early stages of chronic kidney disease is critical to good patient outcome. Levin notes, however, that under the current state of the art,

most patients are referred to nephrologists too late in the course of their renal disease for improvement. As a consequence of these late referrals to nephrologists, there is a significant increase in patient morbidity, mortality and resource utilization.

Such dire consequences would be avoidable if an adequate method for the diagnosis/prognosis of kidney disease existed. In this regard, Levin expressly blames the insensitivity of current screening tools for causing late referrals: "Reasons for late referral include **insensitivity of current screening tools**. Serum creatinine is well known to be an **inaccurate marker of renal dysfunction**, and too insensitive to identify patients with very early stages of disease, thus contributing to the prevalence of late referrals (emphasis added)." *See*, page 8, left column, 4th paragraph. See also, page 10, right column, 1st paragraph, where Levin states: "However, current patterns of 'late referrals' may reflect, at least in part, **difficulties with today's screening tools** (emphasis added)."

Again, the consequences of these late referrals are dire: "The consequences of late referrals include **increased morbidity, mortality and resource utilization.** There is also an impact on patients' quality of life and **missed opportunities** for pre-emptive transplantation (emphasis added)." *See*, page 8, right column, 2nd paragraph. As such,

the art recognizes that there is a direct correlation between the current deficiencies in the art and poor outcome for patients suffering from kidney disease.

Levin goes on to expressly state that poor patient outcome caused by late referral could be avoided if there were an adequate method for diagnosing kidney disease: "The first step in ensuring timely referral of patients to nephrologists is the **implementation of sensitive screening tools** (emphasis added)." *See*, page 10, left column, 2nd paragraph, last 3 lines.

Given the above statements, Levin recognizes the persistent need that exists in the art for a method for the diagnosis or prognosis of kidney disease in a human. Levin further evidences that this need was well recognized by those of ordinary skill in the art. Thus, the current development of a more practical screening tool (i.e., method for diagnosis/prognosis of kidney disease) represents a significant advance in the art.

8. The long-felt need in the art for a method for the diagnosis or prognosis of kidney disease in a human was not satisfied by another before the presently claimed invention was invented by my co-inventors and I.

The diagnostic techniques currently employed to screen for kidney disease all have various defects as described in, for example, Caramori et al., "Perspectives in Diabetes: The need for early predictors of diabetic nephropathy risk. Is albumin excretion rate sufficient?" *Diabetes*, 49:1399-1408, September 2000 (attached hereto as **Exhibit C**), and Rodrigo et al., "Measurement of renal function in pre-ESRD [end-stage renal disease] patients" *Kidney International*, 61(Suppl.80):S11-S17, 2002 (attached hereto as **Exhibit D**).

Specifically, Caramori et al. evidences that the current method of measuring albumin excretion rate, which is currently the best available noninvasive predictor of diabetic nephropathy (DN) risk, is still insufficient under many circumstances:

> However, AFR (albumin excretion rate) may be unable to define patients who are safe from or at risk of DN with an accuracy that is adequate for optimal clinical decision making or for the design of certain clinical trials. Investigations into new risk markers or into the combined use of several currently available predictive parameters are needed.

See, page 1399, left column, line 3 from the bottom to right column, line 4.

In addition, Rodrigo et al. evidences that the most reliable methods currently used in the art are deficient:

> The most reliable methods, such as inulin clearance or measurement by radioisotopes, are too awkward for the usual clinical follow-up of patients...The determinations of the plasmatic creatinine and its clearance or the estimate of the glomerular filtration rate by means of equations derived from the creatinine are the methods most often used in order to measure renal function, although not without problems in pre-dialysis. In order to try to overcome such problems, more precise equations and procedures, including the measurement of averaged urea-creatinine clearance or creatinine clearance with cimetidine, have been designed that better estimate the glomerular filtration rate. **However, none of these methods is totally reliable in pre-dialysis** (emphasis added).

See, page S11, left column.

Since the diagnosis/prognosis of kidney disease is very important for determining the most suitable method for treatment, a new method for the diagnosis/prognosis has earnestly been desired in the art. Nevertheless, no satisfactory method for the diagnosis or prognosis of kidney disease has ever been disclosed prior to the filing of the present patent application. In fact, the present invention can be used not only for diagnosis but also for the prognosis of kidney disease, which hitherto has been very difficult. Hence, the present invention is extremely effective and useful in a practical standpoint.

9. The present invention in fact satisfies the long-felt need in the art for a method for diagnosis/prognosis of kidney disease in a human.

The claimed method of the present invention is vastly superior over the existing methods. The effectiveness and usefulness of the present invention are clear from the data published in Kamijo et al., *J. Lab. Clin.* Med. 143(1):23-30, 2004 (already of record in the present application).

In Kamijo et al., the correlation of diagnostic markers, including L-FABP of the method of the present invention, with the progression rate of renal disease was statistically analyzed in patients with chronic kidney disease. The clinical test results are shown in Table III and page 26, left column, last line to the right column, line 8. The "F ratio" in Table III stands for the correlation with "progression rate." This means that the larger the F ratio, the higher the correlation. As is clear from the test results, among the various diagnostic markers (e.g., serum creatinine, urinary protein, NAG, α1-MG, etc.), **only L-FABP had a statistically significant high F ratio (F ratio = 17.1)**. On the other hand, all of the other diagnostic markers only had an F ratio of between 0.1 and 2.0. These results unequivocally prove that L-FABP has a very high correlation with the progression rate

of renal disease.

In the abstract, Kamijo et al. states, "The results showed that urinary L-FABP reflected the clinical prognosis of chronic renal disease. Urinary L-FABP may be a clinical marker that can help predict the progression of chronic glomerular disease." See, page 23, abstract, lines 19-22. Thus, it has been confirmed that the method of the present invention is superior and can also be applied to prognosis of kidney disease.

As is further noted in Kamijo et al., the method of the present invention has been subjected to clinical tests and applications for the development of new diagnostic reagents in Japan and now plans are in place for clinical tests also in the United States.

When the present invention is used clinically, it will highly contribute to the remedy of the kidney disease and then to resolution of the social problems due to the kidney disease as mentioned above.

10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Signed this day 10 of May, 2005

Takeshi Sugaya

Takeshi SUGAYA